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Short Research Article

Automated PET radiosyntheses using microfluidic devices†

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Introduction

Microfluidic devices can be used to achieve rapid synthesis times whilst providing a highly controlled reaction environment. These factors, in conjunction with their small size and reduced reagent consumption, make them well suited for application to automated PET radiosynthesis.[1,2]

To successfully exploit a microfluidic device for automated PET radiosynthesis, several factors need to be taken into account, such as: fluidic device material; adaption of a batch process to a flow environment; interface between the macroscale (cyclotron target) and the microscale (fluidic device); linking of stages to conduct successive radiochemical processes and optimal design to achieve desired radiochemical yield and purity. Consideration of these issues will determine whether an automated radiosynthesis can be successfully conducted on the microscale.

To address some of these issues, a number of automated radiolabelling reactions have been conducted using microfluidic devices coupled to macroscale automated hardware in order to ascertain whether the benefits of microscale devices can still be exploited under fully automated conditions. For the purposes of the evaluation, the radiosynthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose (2-[^{18}F]FDG) was selected as the model reaction.[3]

Results and discussion

Chemical reactions conducted on the microscale offer many advantages over the macroscale, such as improved mixing efficiency, increased reaction speeds, small size, low reagent consumption and controlled reaction environment.[4] These factors would suggest that microfluidic devices are ideally suited for automated PET radiosynthesis.

For a full PET radiosynthesis to be conducted, a series of processes need to be conducted sequentially. Proof of principle that this approach can be applied on the microscale has been reported previously[1] (Figure 1).

Results from the proof of concept experiments demonstrated that rapid reaction times (<20 s) could be attained on the microscale.[2] However, these reaction times were not exploited when the process was translated to an automated system (Figure 2). In the example shown, flow rates of 5–10 μl/min were used to transfer reagent solutions through two microfluidic devices linked in series. With reagent volumes of 300 μl, the total process time was 30–60 min, which did not include the preparation of an anhydrous [^{18}F]fluoride solution.

To address some of these issues, a fully automated platform was developed for the [^{18}F]fluoridation and deprotection synthesis of 2-[^{18}F]FDG incorporating a single two-stage microfluidic device with localized heating (Figure 3). The microfabricated device was constructed from glass to avoid any solvent incompatibility issues.

To simplify the automated processing, conventional [^{18}F]fluoride processing apparatus was utilized. The reaction vessel was used as the interface between the macroscale (cyclotron target) and the microscale

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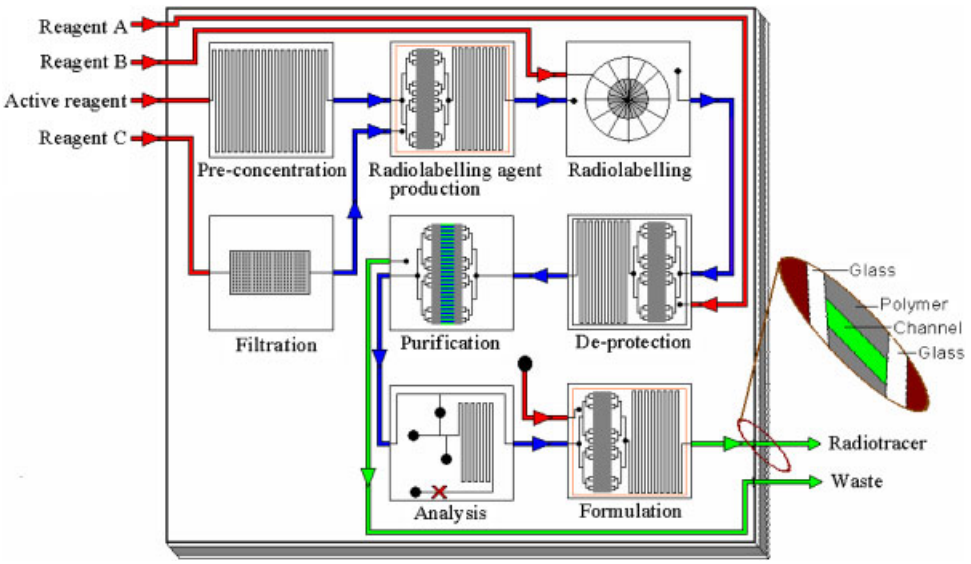

Figure 1 Illustration of a miniaturized radiosynthesis system on a microfabricated device. Figure available in colour online at www.interscience.wiley.com

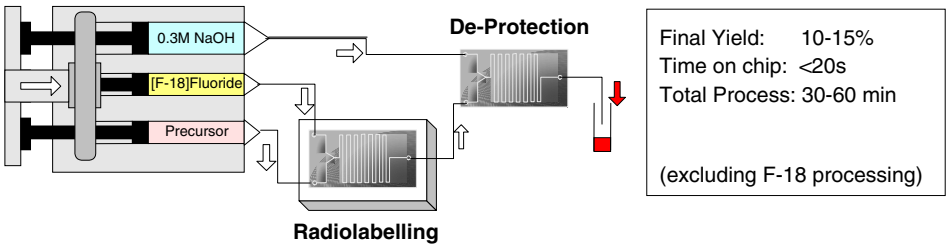

Figure 2 Schematic diagram of apparatus utilized for conducting a two-stage automated 2-[^{18}F]FDG synthesis on two separate microfluidic devices. Figure available in colour online at www.interscience.wiley.com

(fluidic device). Incorporation of the microfluidic device into an automated platform simplified the 2-[^{18}F]FDG radiosynthesis enabling both fluoridation and deprotection reactions to be conducted sequentially as a single process. A summary of the results obtained from the preliminary experiments is shown in Table 1.

At a flow rate of 50 µl/min, 2-[^{18}F]FDG yields of 20% were obtained in 9 s (radiolabelling yield: 25% in 6 s; deprotection yield: 80% in 3 s). With initial reagent volumes of 500 µl, the total time taken to transfer the reagents through the microfluidic device was 10 min. The total synthesis time inclusive of [^{18}F]fluoride processing was 18 min.

When parameters such as precursor quantity, reaction temperature and flow rate were varied, the radiochemical yield of 2-[^{18}F]FDG was found to be extremely reproducible thus demonstrating the controlled microfluidic reaction environment. Since the process was fully automated, starting activities in the range of 1 mCi to 1 Ci of [^{18}F]fluoride were used. No radiolysis was observed when 1 Ci of [^{18}F]fluoride was used, demonstrating the proof of concept that patient doses can be delivered from microfluidic-based automated apparatus. No evidence of the decomposition product 2-deoxy-2-[^{18}F]fluoro-D-mannose was observed demonstrating that heating was well localized within the fluidic device and that good radiochemical product purity could be obtained.

Differing microfluidic devices were utilized to enable faster reagent transfer flow rates to be utilized. Results from these experiments demonstrated that improved system performance could be obtained (Table 2).

At a flow rate of 250 µl/min, 2-[^{18}F]FDG yields of 40% were obtained. Total transition time was 4 min whilst total synthesis time was 10 min inclusive of [^{18}F]fluoride processing. These results demonstrate the proof of concept that system performances comparable with

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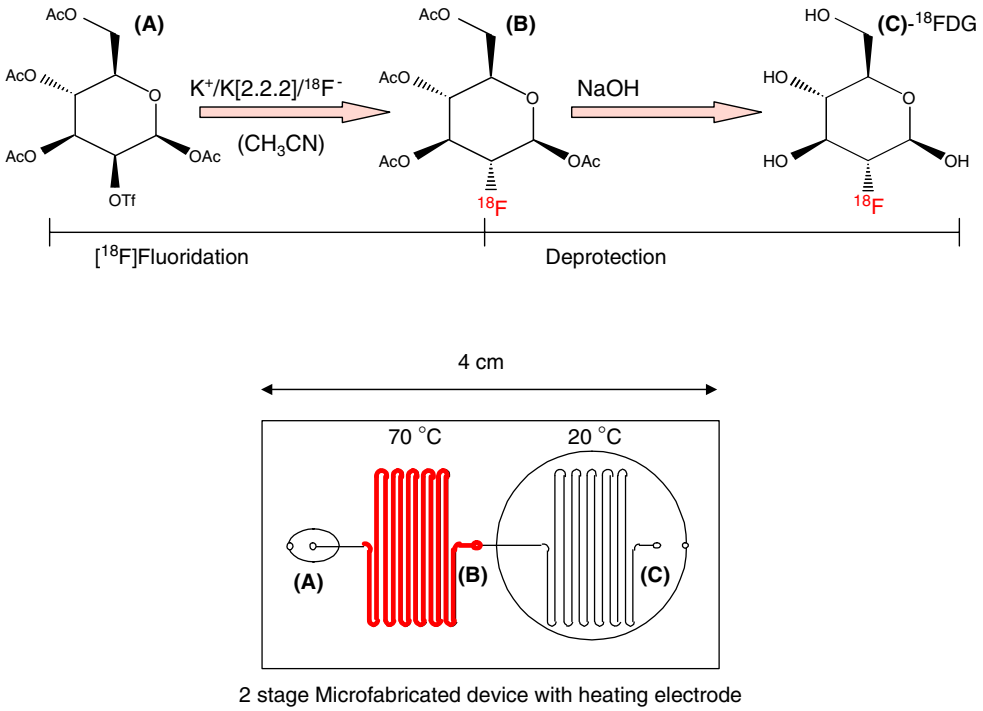

Figure 3 Overview of a two-stage microfluidic device for sequential [^{18}F]fluoridation and deprotection synthesis of 2-[^{18}F]FDG. Figure available in colour online at www.interscience.wiley.com

Table 1 Preliminary experimental results obtained from the radiosynthesis of 2-[^{18}F]FDG using a dual-stage microfluidic device

Reaction parameters		2-[^{18}F]FDG yield/'on-chip' reaction time	
Reagent volumes	500 µl	Radiolabelling reaction	25% (6 s)
MFD transfer flow rate	50 µl/min	Deprotection reaction	80% (3 s)
MFD transit time	9 s	Total 2-[^{18}F]FDG synthesis	20% (9 s)
Total MFD transfer time	10 min		
Total process time	18 min		

Parameter varied	Range	2-[^{18}F]FDG yield (%)
Triflate mass	40–5 mg	20%
Temperature	65–95 °C	20%
MFD transfer flow rate	20–55 µl/min	20%
Starting radioactivity	1–1000 mCi	20%

Table 2 Results obtained from the radiosynthesis of 2-[^{18}F]FDG conducted using differing microstructures

Total process time	
[^{18}F$^-$]drying/phase transfer	6 min
Radiolabelling reaction	2 min
Deprotection reaction	2 min
Total 2-[^{18}F]FDG synthesis	10 min
2-[^{18}F]FDG yield (decay corrected)	40%

commercial platforms may be feasible from microfluidic-based radiosynthesis platforms.

Conclusion

Results demonstrate that the benefits of using microfluidic devices can still be exploited under fully automated radiosynthesis conditions. The results further demonstrate that system performances

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comparable with commercial platforms may be feasible from microfluidic-based radiosynthesis platforms and that patient doses can provided from these platforms.

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